DIAZABICYCLONONENE AND TETRAHYDROPYRIDINE DERIVATIVES AS RENIN INHIBITORS

The invention relates to novel five-membered heteroaryl derivatives of the general formula (I). The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I) and especially their use as renin inhibitors in cardiovascular events and renal insufficiency.

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT_1 and AT_2. Whereas AT_1 seems to transmit most of the known functions of Ang II, the role of AT_2 is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT_1 blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Berkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, **1996**, 489-519; Weber M. A., *Am. J. Hypertens.*, **1992**, *5*, 247S). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney International*, **1994**, *45*, 403; Breyer J. A. *et al.*, *Kidney International*, **1994**, *45*, S156), in the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, **1994**, *28*, 159; Fouad-Tarazi F. *et al.*, *Am. J. Med.*, **1988**, *84 (Suppl. 3A)*, 83) and myocardial infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, **1992**, *327*, 669).

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening

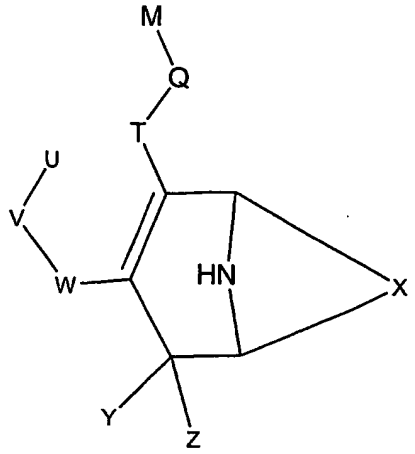
angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, **1992**, *117*, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT_1 receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT_2) to Ang II, whose concentration is significantly increased by the blockade of AT_1 receptors. In summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT_1 blockers with regard to efficacy in blocking the RAS and in safety aspects.

Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, *12*, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, *122*, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, **2000**, *7*, 493; Mealy N. E., *Drugs of the Future*, **2001**, *26*, 1139). Thus, renin inhibitors with good oral bioavailability and long duration of action are required. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, **1999**, *6*, 127; Patent Application WO97/09311; Märki H. P. *et al.*, *Il Farmaco*, **2001**, *56*, 21). However, the development status of these compounds is not known.

The present invention relates to the identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Described are orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodeling, atherosclerosis, and possibly restenosis. So, the present invention describes these non-peptidic renin inhibitors.

The present invention describes non-peptidic renin inhibitors.

In particular, the present invention relates to novel compounds of the general formula **I**,



Formula I

wherein

Y and Z represent independently hydrogen, fluorine or a methyl group, or Y and Z may together form a cyclopropyl ring;

X represents $-CH_2-CH(K)-CH_2-$; $-CH_2CH_2-$; $-CH_2OCH_2-$; $-CH_2SCH_2-$; $-CH_2SOCH_2-$; $-CH_2SO_2CH_2-$; $-CO-NL-CHR^6-$; $-CHR^6-NL-CO-$;

W represents a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in position 3 or 4;

V represents a bond; $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; $-CH_2-CH_2-A-CH_2-CH_2-B-$; $-O-CH_2-CH(OCH_3)-CH_2-O$; $-O-CH_2-CH(CH_3)-CH_2-O-$; $-O-CH_2-CH(CF_3)-CH_2-O-$; $-O-CH_2-C(CH_3)_2-CH_2-O-$; $-O-CH_2-C(CH_3)_2-O-$; $-O-C(CH_3)_2-CH_2-O-$; $-O-CH_2-CH(CH_3)-O-$; $-O-CH(CH_3)-CH_2-O-$; $-O-CH_2-C(CH_2CH_2)-O-$; $-O-C(CH_2CH_2)-CH_2-O-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents aryl-$O(CH_2)_vR^5$; heteroaryl-$O(CH_2)_vR^5$; aryl-$O(CH_2)_2O(CH_2)_wR^5$; heteroaryl-$(CH_2)_2O(CH_2)_wR^5$;

L represents $-R^3$; $-COR^3$; $-COOR^3$; $-CONR^2R^3$; $-SO_2R^3$; $-SO_2NR^2R^3$; $-COCH(Aryl)_2$;

K represents –H; -CH_2OR^3; -$CH_2NR^2R^3$; -$CH_2NR^2COR^3$; -$CH_2NR^2SO_2R^3$; -CO_2R^3; -$CH_2OCONR^2R^3$; -$CONR^2R^3$; -$CH_2NR^2CONR^2R^3$; -$CH_2SO_2NR^2R^3$; -CH_2SR^3; -CH_2SOR^3; -$CH_2SO_2R^3$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, -$OCOR^2$, -$COOR^2$, lower alkoxy, cyano, -$CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -$COOR^2$; -$CONH_2$;

R^5 represents –OH, -$OCOR^2$, -$COOR^2$, -$NR^2R^{2'}$, -$OCONR^2R^{2'}$, -$NCONR^2R^{2'}$, cyano, -$CONR^2R^{2'}$, SO_3H, -$SONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^6 represents hydrogen; lower alkyl; lower alkoxy, whereby these groups may be unsubstituted or monosubstituted with hydroxy, -$CONH_2$, -COOH, imidazoyl, -NH_2, -CN, -$NH(NH)NH_2$;

p is the integer 1, 2, 3 or 4;

r is the integer 1, 2, 3, 4, 5, or 6;

s is the integer 1, 2, 3, 4, or 5;

t is the integer 1, 2, 3, or 4;

u is the integer 1, 2, or 3;

v is the integer 2, 3, or 4;

w is the integer 1 or 2.

In addition optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of

diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms are also encompassed by the present invention.

In the definitions of general formula **I** – if not otherwise stated – the term **lower alkyl**, alone or in combination with other groups, means saturated, straight and branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms that can be optionally substituted by halogens. Examples of lower alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

The term **lower alkoxy** refers to a R-O group, wherein R is a lower alkyl. Examples of lower alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term **lower alkenyl**, alone or in combination with other groups, means straight and branched chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenyl are vinyl, propenyl or butenyl.

The term **lower alkinyl**, alone or in combination with other groups, means straight and branched chain groups comprising a triple bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkinyl are ethinyl, propinyl or butinyl.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkylene are methylene ethylene, propylene or butylene. In another embodiment of the invention lower alkylene means ethylene, propylene or butylenes. In another embodiment of the invention lower alkylene means methylene.

The term **lower alkenylene**, alone or in combination with other groups, means straight and branched divalent chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms, that can be optionally substituted by halogens. Examples of lower alkenylene are vinylene, propenylene and butenylene.

The term **lower alkylenedioxy**, refers to a lower alkylene substituted at each end by an oxygen atom. Examples of lower alkylenedioxy groups are preferably methylenedioxy and ethylenedioxy.

The term **lower alkylenoxy** refers to a lower alkylene substituted at one end by an oxygen atom. Examples of lower alkylenoxy groups are preferably methylenoxy, ethylenoxy and propylenoxy.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine and bromine.

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkenylene, lower alkoxy, lower alkylenoxy, lower alkylenedioxy, hydroxy, halogen, $-CF_3$, $-NR^1R^{1'}$, $-NR^1COR^{1'}$, $-NR^1SO_2R1'$, $-CONR^1R^{1'}$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$ whereby $R^{1'}$ represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl. The cyclopropyl group is a preferred group.

The term **aryl**, alone or in combination, relates to the phenyl, the naphthyl or the indanyl group, preferably the phenyl group, which can be optionally mono- or multisubstituted by lower alkyl, lower alkenyl, lower alkinyl, lower alkenylene or lower alkylene forming with the aryl ring a five- or six-membered ring, lower alkoxy, lower alkylenedioxy, lower alkylenoxy, hydroxy, hydroxy-lower alkyl, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-NR^1COR^{1'}$, $-NR_1SO_2R^1$, $-CONR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$, benzyloxy, whereby $R^{1'}$ has the meaning given above.

For the substituent U, the term aryl means 2-chloro-3,6-difluorophenyl or 2,6-dichloro-4-methylphenyl.

The term **aryloxy** refers to an Ar-O group, wherein Ar is an aryl. An example of a lower aryloxy group is phenoxy.

The term **heterocyclyl**, alone or in combination, means saturated or unsaturated (but not aromatic) five-, six- or seven-membered rings containing one or two nitrogen, oxygen or

sulfur atoms which may be the same or different and which rings can be optionally substituted with lower alkyl, hydroxy, lower alkoxy and halogen. The nitrogen atoms, if present, can be substituted by a -$COOR^2$ group. Examples of such rings are piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, dihydropyranyl, 1,4-dioxanyl, pyrrolidinyl, tetrahydrofuranyl, dihydropyrrolyl, imidazolidinyl, dihydropyrazolyl, pyrazolidinyl, dihydroquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl.

The term **heteroaryl**, alone or in combination, means six-membered aromatic rings containing one to four nitrogen atoms; benzofused six-membered aromatic rings containing one to three nitrogen atoms; five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; benzofused five-membered aromatic rings containing one oxygen, one nitrogen or one sulfur atom; five-membered aromatic rings containing one oxygen and one nitrogen atom and benzofused derivatives thereof; five-membered aromatic rings containing a sulfur and a nitrogen or an oxygen atom and benzofused derivatives thereof; five-membered aromatic rings containing two nitrogen atoms and benzofused derivatives thereof; five-membered aromatic rings containing three nitrogen atoms and benzofused derivatives thereof, or a tetrazolyl ring. Examples of such ring systems are furanyl, thiophenyl, pyrrolyl, pyridinyl, pyrimidinyl, indolyl, quinolinyl, isoquinolinyl, imidazolyl, triazinyl, thiazinyl, thiazolyl, isothiazolyl, pyridazinyl, pyrazolyl, oxazolyl, isoxazolyl, coumarinyl, benzothiophenyl, quinazolinyl, quinoxalinyl. Such rings may be adequatly substituted with lower alkyl, lower alkenyl, lower alkinyl, lower alkylene, lower alkenylene, lower alkylenedioxy, lower alkyleneoxy, hydroxy-lower alkyl, lower alkoxy, hydroxy, halogen, cyano, $-CF_3$, $-OCF_3$, $-NR^1R^{1'}$, $-NR^1R^{1'}$ - lower alkyl, $-N(R^1)COR^1$, $-N(R^1)SO_2R^1$, $-CONR^1R^{1'}$, $-NO_2$, lower alkylcarbonyl, $-COOR^1$, $-SR^1$, $-SOR^1$, $-SO_2R^1$, $-SO_2NR^1R^{1'}$, another aryl, another heteroaryl or another heterocyclyl and the like, whereby $R^{1'}$ has the meaning given above.

For the substituent M, the term heteroaryl means 3-methyl-pyridin-4-yl.

The term **heteroaryloxy** refers to a Het-O group, wherein Het is a heteroaryl group.

The term **cycloalkyl - lower alkyl** refers to a cycloalkyl group as defined above which is substituted with a lower alkyl group.

The term **aryl - lower alkyl** refers to an aryl group as defined above which is substituted with a lower alkyl group.

The term **heteroaryl - lower alkyl** refers to a heteroaryl group as defined above which is substituted with a lower alkyl group.

The term **heterocyclyl - lower alkyl** refers to a heterocyclyl group as defined above which is substituted with a lower alkyl group.

The term **aryloxy - lower alkyl** refers to a Ar-O group as defined above which is substituted with a lower alkyl group.

The term **heteroaryloxy - lower alkyl** refers to a Het-O group as defined above which is substituted with a lower alkyl group.

The term **hydroxy - lower alkyl** refers to a lower alkyl group as defined above which is substituted with a hydroxyl group.

The term **lower alkylcarbonyl** refers to a lower alkyl-CO- group.

The term **sp3-hybridized** refers to a carbon atom and means that this carbon atom forms four bonds to four substituents placed in a tetragonal fashion around this carbon atom.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic acid, and the like that are non toxic to living organisms or in case the compound of formula **I** is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like.

The compounds of the general formula **I** can contain two or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form and pharmaceutically acceptable salts thereof.

The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization.

Another group of preferred compounds of general formula I are those wherein Z, Y, W, V, U, T, Q, and M are as defined in general formula I above and
X represents $-CH_2CH_2-$.

Another group of preferred compounds of general formula I are those wherein Z, Y, X, W, V, U, T, Q, and M are as defined in general formula I above and
L represents H; $-COR^{3''}$; $-COOR^{3''}$; $-CONR^{2''}R^{3''}$;
whereby $R^{2''}$ and $R^{3''}$ represent independently lower alkyl, lower cycloalkyl - lower alkyl, which lower alkyl and lower cycloalkyl - lower alkyl groups are unsubstituted or monosubstituted with halogen, cyano, hydroxy, $-OCOCH_3$, $-CONH_2$, -COOH, $-NH_2$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized.

Another group of preferred compounds of general formula I above are those wherein Z, Y, X, W, V, and U are as defined in general formula I and
T is $-CONR^1-$;
Q is methylene;
M is aryl-$O(CH_2)_vR^5$; heteroaryl-$O(CH_2)_vR^5$.

Another group of also more preferred compounds of general formula I are those wherein Z, Y, X, V, U, T, Q, and M are as defined in general formula I above and
W represents a 4-substituted phenyl.

Another group of also more preferred compounds of general formula I are those wherein Z, Y, X, W, V, Q, T, and M are as defined in general formula I above and
U is a mono-, di-, or trisubstituted phenyl wherein the substituents are halogen; lower alkyl or lower alkoxy.

A most preferred group of compounds of formula I are those wherein
Z and Y represent hydrogen;
U represents a tri-substituted phenyl ring substituted independently with halogen or C_1-C_4-alkyl;

V represents –O-CH_2-CH_2-CH_2-; -O-CH_2-CH_2-O-; -O-CH_2-CH_2-; -CH_2- CH_2-O-; -O-CH_2-CH_2-CH_2-O-; -CH_2-CH_2-CH_2-O-;

W represents a phenyl ring substituted by V in the 4-position and connected to the carbon atom at the double bond of the tetrahydro-pyridin ring in the 1-position;

X represents –CH_2-CH_2-; -CH_2- SO-CH_2-; - CH_2- SO_2-CH_2-; -CH_2-O-CH_2-;

T represents –$CONR^1$-, wherein R^1 is a cycloalkyl group;

Q represents –CH_2-;

M represents a substituted pyridyl-$O(CH_2)_vR^5$ group substituted with C_1-C_4-alkyl, wherein R^5 is hydroxyl; -$COOR_2$, wherein R^2 is hydrogen or C_1-C_4-alkyl; or –$CONR^2R^{2'}$, wherein R^2 and $R^{2'}$ are hydrogen or C_1-C_4-alkyl.

Another most preferred group of compounds of formula I are those wherein

Z and Y represent hydrogen;

U represents a tri-substituted phenyl ring substituted independently with halogen or a phenyl ring substituted in 2- and 6- position with chloro and in 4-position with a methyl group;

V represents –O-CH_2-CH_2-CH_2-; -O-CH_2-CH_2-O-;

W represents a phenyl ring substituted by V in the 4-position and connected to the carbon atom at the double bond of the tetrahydro-pyridin ring in the 1-position;

X represents –CH_2-CH_2-; - CH_2- SO_2-CH_2-; -CH_2-O-CH_2-;

T represents –$CONR^1$-, wherein R^1 is a cyclopropyl group;

Q represents –CH_2-;

M represents a pyridinyl-$O(CH_2)_vR^5$ group, whereby the pyridinyl ring is substituted with a methyl group, wherein R^5 represents hydroxyl; or -$COOR_2$, wherein R^2 is hydrogen or methyl; or R^5 is –$CONH_2$ and $_v$ is the integer 2 or 3.

In another embodiment of the invention p is the integer 1 or 2.

In another embodiment of the invention r is the integer 1, 2, or 3.

In another embodiment of the invention s is the integer 1, 2 or 3.

In another embodiment of the invention t is the integer 3.

In another embodiment of the invention u is the integer 1 or 2.

In another embodiment of the invention v is the integer 2 or 3.

In another embodiment of the invention w is the integer 1.

In another embodiment of the invention w is the integer 2.

In another embodiment of the invention A and B independently represent -O-.

In another embodiment of the invention, the substituent R^2 represent OH or methyl.
In another embodiment of the invention, the substituent R^5 represent –OH, -$COOR^2$ or -$CONR^2R^{2'}$ (wherein R^2 and $R^{2'}$ are hydrogen).

Especially preferred compounds of general formula I are those selected from the group consisting of:

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-hydroxypropoxy)-3-methylpyridin-4-ylmethyl]amide,

(*rac.*)-(*1R**, *5S**)-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-hydroxypropoxy)-3-methylpyridin-4-ylmethyl]amide,

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,3-dioxo-3λ^6-thia-9-azabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxypropoxy)-3-methylpyridin-4-ylmethyl]amide,

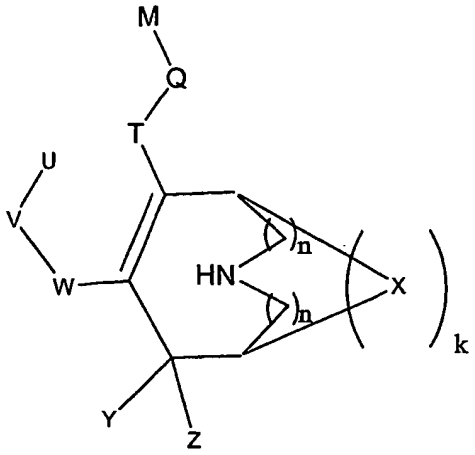
(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3-oxa-9-azabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide,

(*rac.*)-(*1R**, *5S**)-3-(4-{[(3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]-phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carbonyl)cyclopropylamino]methyl}-3-methyl-pyridin-2-yloxy)propionic acid,

(*rac.*)-(*1R**, *5S**)-3-(4-{[(3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carbonyl)cyclopropylamino]methyl}-3-methyl-pyridin-2-yloxy)propionic acid methyl ester, and

(*rac.*)-(*1R**, *5S**)-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid [2-(2-carbamoylethoxy)-3-methyl-pyridin-4-ylmethyl]cyclopropylamide.

Another embodiment of the invention are compounds of the general formula I



Formula I

wherein

Y and Z represent independently from each other hydrogen, fluorine or a methyl group, or Y and Z may together form a cyclopropyl ring; in case k represents the integer 1, Y and Z both represent hydrogen;

X represents $-(CH_2)_m-N(L)-(CH_2)_m-$; $-CH_2-CH(K)-CH_2-$; $-CH_2CH_2-$; $-CH_2OCH_2-$; $-CH_2SCH_2-$; $-CH_2SOCH_2-$; $-CH_2SO_2CH_2-$; -CO-NL-CO-; $-CO-NL-CHR^6-$; $-CHR^6-NL-CO-$;

W represents a six-membered, non benzofused, phenyl or heteroaryl ring, substituted by V in position 3 or 4;

V represents a bond; $-(CH_2)_r-$; $-A-(CH_2)_s-$; $-CH_2-A-(CH_2)_t-$; $-(CH_2)_s-A-$; $-(CH_2)_2-A-(CH_2)_u-$; $-A-(CH_2)_v-B-$; $-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-B-$; $-CH_2-CH_2-CH_2-A-CH_2-CH_2-$; $-CH_2-CH_2-CH_2-CH_2-A-CH_2-$; $-A-CH_2-CH_2-B-CH_2-CH_2-$; $-CH_2-A-CH_2-CH_2-B-CH_2-$; $-CH_2-A-CH_2-CH_2-CH_2-B-$; or $-CH_2-CH_2-A-CH_2-CH_2-B-$; $-O-CH_2-CH(OCH_3)-CH_2-O$; $-O-CH_2-CH(CH_3)-CH_2-O-$; $-O-CH_2-CH(CF_3)-CH_2-O-$; $-O-CH_2-C(CH_3)_2-CH_2-O-$; $-O-CH_2-C(CH_3)_2-O-$; $-O-C(CH_3)_2-CH_2-O-$; $-O-CH_2-CH(CH_3)-O-$; $-O-CH(CH_3)-CH_2-O-$; $-O-CH_2-C(CH_2CH_2)-O-$; $-O-C(CH_2CH_2)-CH_2-O-$;

A and B independently represent -O-; -S-; -SO-; $-SO_2-$;

U represents aryl; heteroaryl;

T represents $-CONR^1-$; $-(CH_2)_pOCO-$; $-(CH_2)_pN(R^1)CO-$; $-(CH_2)_pN(R^1)SO_2-$; or -COO-;

Q represents lower alkylene; lower alkenylene;

M represents aryl-$O(CH_2)_vR^5$; heteroaryl-$O(CH_2)_vR^5$; aryl-$O(CH_2)_2O(CH_2)_wR^5$; heteroaryl-$(CH_2)_2O(CH_2)_wR^5$;

L represents $-R^3$; $-COR^3$; $-COOR^3$; $-CONR^2R^3$; $-SO_2R^3$; $-SO_2NR^2R^3$;

-$COCH(Aryl)_2$;

K represents –H; -CH_2OR^3; -$CH_2NR^2R^3$; -$CH_2NR^2COR^3$; -$CH_2NR^2SO_2R^3$; -CO_2R^3; -$CH_2OCONR^2R^3$; -$CONR^2R^3$; -$CH_2NR^2CONR^2R^3$; -$CH_2SO_2NR^2R^3$; -CH_2SR^3; -CH_2SOR^3; -$CH_2SO_2R^3$;

R^1 represents hydrogen; lower alkyl; lower alkenyl; lower alkinyl; cycloalkyl; aryl; cycloalkyl - lower alkyl;

R^2 and $R^{2'}$ independently represent hydrogen; lower alkyl; lower alkenyl; cycloalkyl; cycloalkyl - lower alkyl;

R^3 represents hydrogen; lower alkyl; lower alkenyl; cycloalkyl; aryl; heteroaryl; heterocyclyl; cycloalkyl - lower alkyl; aryl - lower alkyl; heteroaryl - lower alkyl; heterocyclyl - lower alkyl; aryloxy - lower alkyl; heteroaryloxy - lower alkyl, whereby these groups may be unsubstituted or mono-, di- or trisubstituted with hydroxy, -$OCOR^2$, -$COOR^2$, lower alkoxy, cyano, -$CONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH^2$, -$NR^4R^{4'}$ or lower alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^4 and $R^{4'}$ independently represent hydrogen; lower alkyl; cycloalkyl; cycloalkyl - lower alkyl; hydroxy - lower alkyl; -$COOR^2$; -$CONH_2$;

R^5 represents –OH, -$OCOR^2$, -$COOR^2$, -$NR^2R^{2'}$, -$OCONR^2R^{2'}$, -$NCONR^2R^{2'}$, cyano, -$CONR^2R^{2'}$, SO_3H, -$SONR^2R^{2'}$, -CO-morpholin-4-yl, -CO-((4-loweralkyl)piperazin-1-yl), -$NH(NH)NH_2$, -$NR^4R^{4'}$, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp3-hybridized;

R^6 represents hydrogen; lower alkyl; lower alkoxy, whereby these groups may be unsubstituted or monosubstituted with hydroxy, -$CONH_2$, -COOH, imidazoyl, -NH_2, -CN, -$NH(NH)NH_2$;

k is the integer 0 or 1;

m and n represent the integer 0 or 1, with the proviso that in case m represents the integer 1, n is the integer 0; in case n represents the integer 1, m is the integer 0; in case k represents the integer 0, n represents the integer 0; in case X does not represent –$(CH_2)_m$-N(L)-$(CH_2)_m$-, n represents the integer 0;

p is the integer 1, 2, 3 or 4;

r is the integer 1, 2, 3, 4, 5, or 6;

s is the integer 1, 2, 3, 4, or 5;

t is the integer 1, 2, 3, or 4;

u is the integer 1, 2, or 3;

v is the integer 2, 3, or 4;

w is th integer 1 or 2;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

The invention relates to a method for the treatment and/or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system, which method comprises administrating a compound as defined above to a human being or animal.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy.

In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases, which are associated with a dysregulation of the renin-angiotensin system as well as for the treatment of the above-mentioned diseases.

The invention also relates to the use of compounds of formula (I) for the preparation of a medicament for the treatment and/or prophylaxis of the above-mentioned diseases.

A further aspect of the present invention is related to a pharmaceutical composition containing at least one compound according to general formula (I) and pharmaceutically

acceptable carrier materials or adjuvants. This pharmaceutical composition may be used for the treatment or prophylaxis of the above-mentioned disorders; as well as for the preparation of a medicament for the treatment and/or prophylaxis of the above-mentioned diseases.

Derivatives of formula (I) or the above–mentioned pharmaceutical compositions are also of use in combination with other pharmacologically active compounds comprising ACE-inhibitors, neutral endopeptidase inhibitors, angiotensin II receptor antagonists, endothelin receptors antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists or with other drugs beneficial for the prevention or the treatment of the above-mentioned diseases.

In a preferred embodiment, this amount is comprised between 2 mg and 1000 mg per day.

In a particular preferred embodiment, this amount is comprised between 1 mg and 500 mg per day.

In a more particularly preferred embodiment, this amount is comprised between 5 mg and 200 mg per day.

All forms of prodrugs leading to an active component comprised by general formula (I) above are included in the present invention.

Compounds of formula (I) and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical compositions containing at least one compound of formula (I) and pharmaceutically acceptable inert carrier material or adjuvants. These pharmaceutical compositions can be used for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e. g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e. g. in the form of suppositories, parenterally, e. g. in the form of injection solutions or infusion solutions, or topically, e. g. in the form of ointments, creams or oils.

The production of pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and their pharmaceutically acceptable acid addition salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together

with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injections are, for example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case.

Another aspect of the invention is related to a process for the preparation of a pharmaceutical composition comprising a derivative of the general formula (I). According to said process, one or more active ingredients of the general formula (I) are mixing with inert excipients in a manner known *per se*.

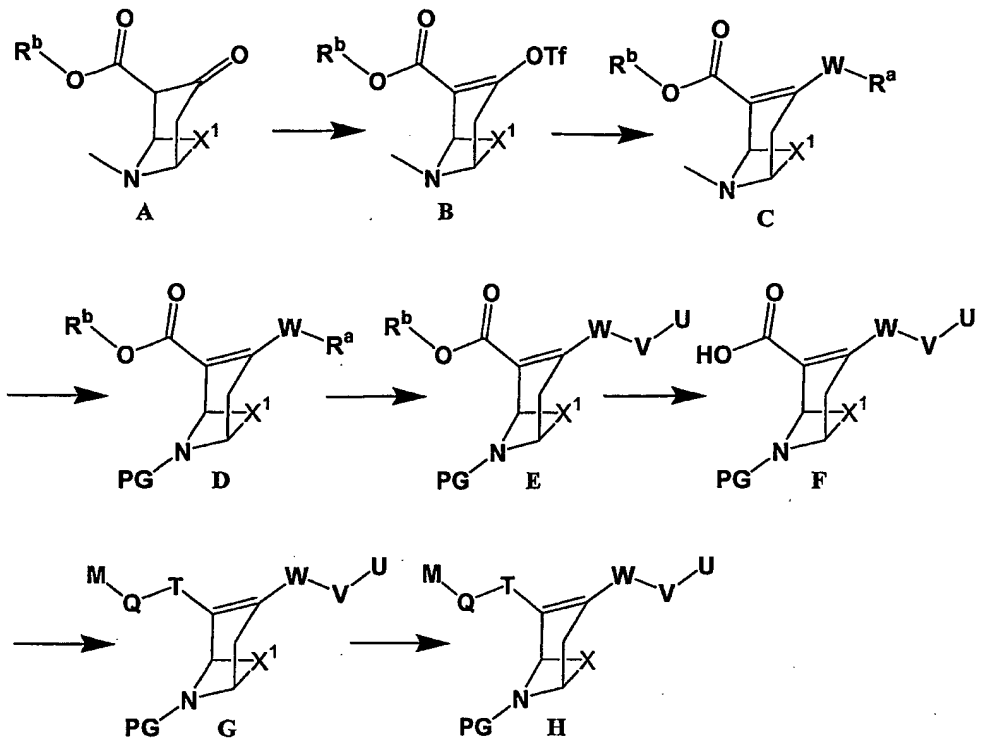
The compounds of general formula I can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

Preparation of the precursors:

Precursors are compounds which were prepared as key intermediates and/or building blocks and which were suitable for further transformations in parallel chemistry. Most of the chemistry applicable here has already been described in the patent applications WO03/093267 and WO04/002957.

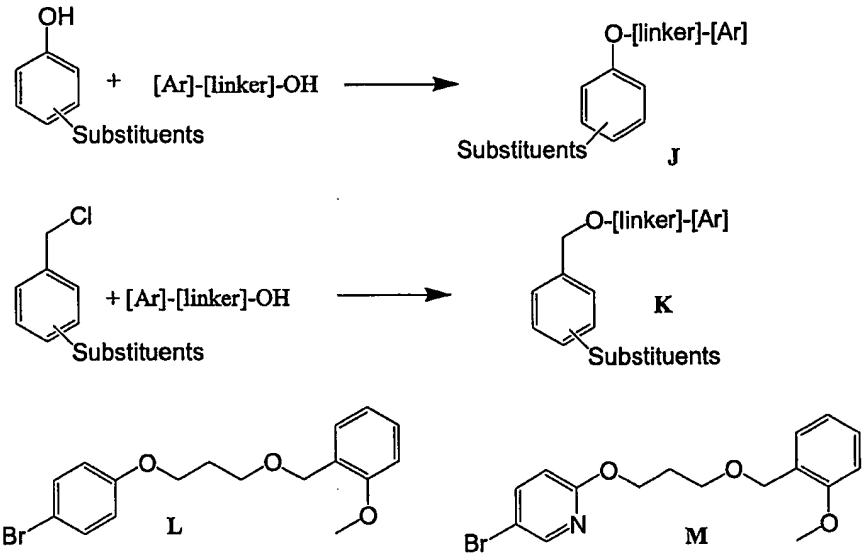
As illustrated in Scheme 1 the known compound **A** can be derivatised into the corresponding triflate **B**. X^1 stands for a precursor of the substituent X as defined in general formula (**I**). The substituent X^1 can be transformed into the substituent X at any stage of the synthesis, whenever convenient. A *Negishi*-type coupling (or any other coupling catalysed by a transition metal) leads to a compound of type **C**, whereas R^a represents a precursor of the substituent U-V as defined in general formula (**I**). R^a can be easily transformed into U-V, using elemental chemical steps. After protecting group manipulation (→ compound of type **D**), ajustement of the W-V-U linker is possible for instance by deprotection and a *Mitsunobu*-type reaction, leading to a compound of type **E**. Hydrolysis of the ester leads to a carboxylic acid of type **F**, then an amide coupling for instance to a compound of type **G**. Removal of the Boc-protecting group and alkylation, or acylation, leads to a precursor of type **H**.

Scheme 1



The bromoaryl components can be prepared as described in Scheme 2. A *Mitsunobu* coupling (→ compounds of type **J**) or the alkylation of an alcohol with a benzylic chloride (or bromide, → compounds of type **K**) are often the most convenient methods. Derivatives **L** and **M** were prepared in one step from 1-(3-chloropropoxymethyl)-2-methoxybenzene (Vieira E. *et al.*, *Bioorg. Med. Chem. Letters*, **1999**, *9*, 1397) or 3-(5-bromopyridin-2-yloxy)propan-1-ol (Patent Application WO 98/39328) according to these methods. Other methods for the preparation of ethers or thioethers, like a *Williamson* synthesis, can be used as well (see e.g. March, J, "Advanced Organic Chemistry,", 3rd ed., John Wiley and sons, 1985).

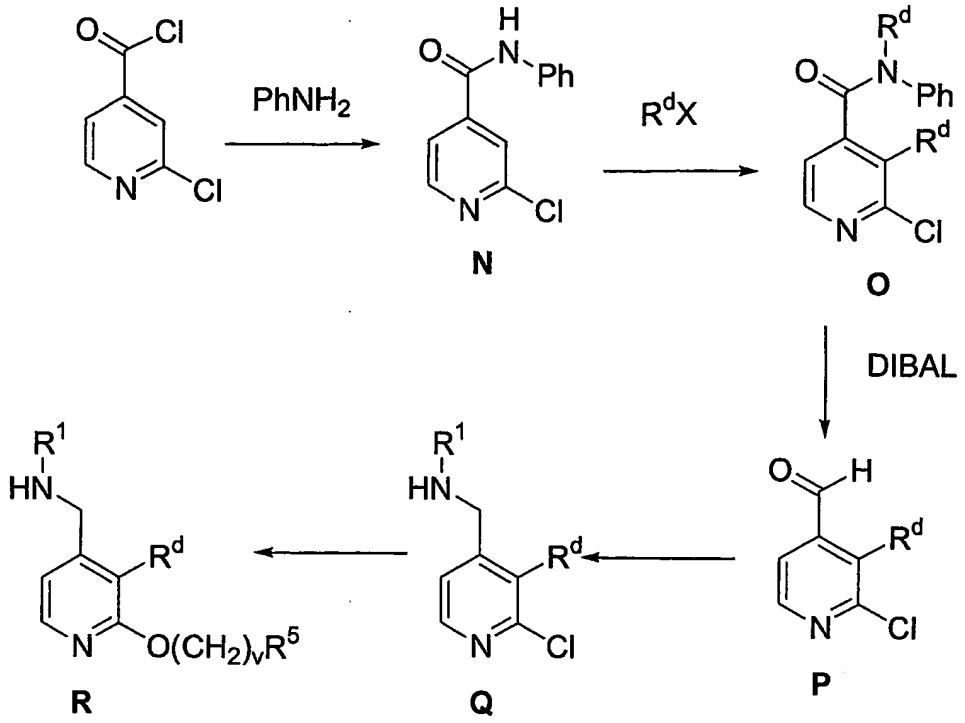
Scheme 2



Preparation of the secondary amines

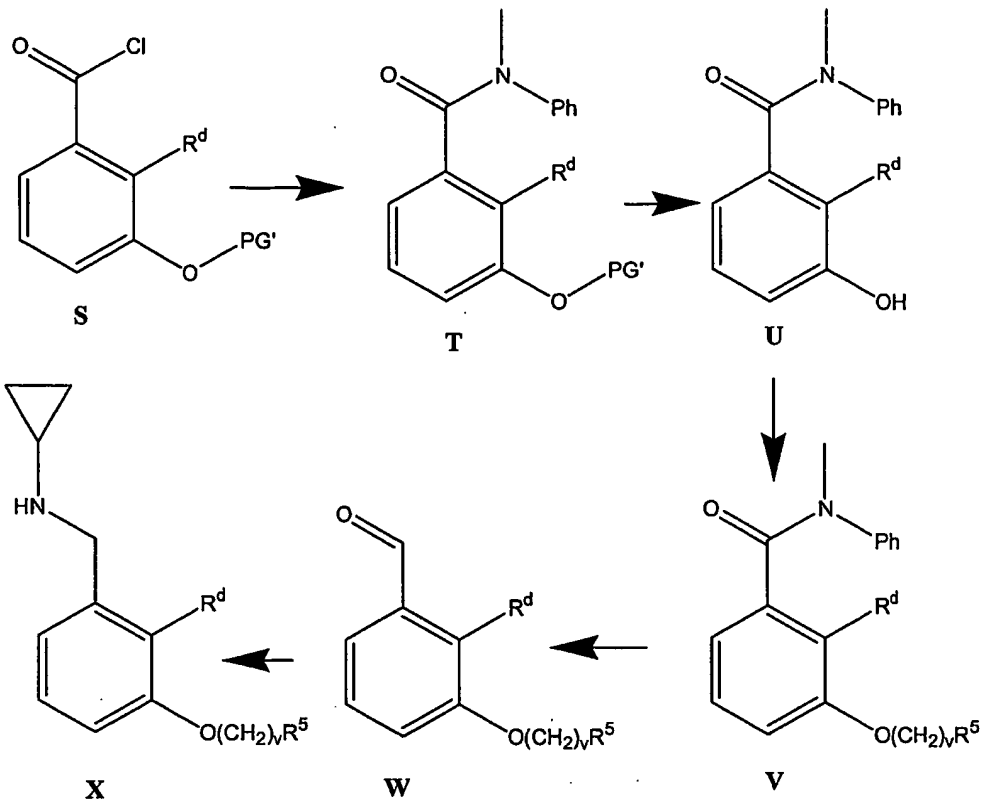
The secondary amines can be prepared for instance as described in Scheme 3. The pyridine derivative **N** can be prepared from commercially available 2-chloro-isonicotinoyl chloride. Deprotonation at the 3-position of this derivative, for instance with BuLi, and subsequent alkylation with a suitable electrophile leads to a derivative of type **O**, whereas R^d represents a suitable substituent that can be introduced by this chemistry, and can be transformed later into a desired substituent a described in general formula **I**. Reduction of the amide into an aldehyde with DIBAL leads to a compound of type **P**, then a reductive amination leads to an amine of type **Q**, whereas R^1 stand for a substituent as defined above. Finally substitution of the chlorine atom with an alcohol of type $HO(CH2)_vR^5$, where as R^5 may still be protected, leads to an amine of type **R**. An alcohol of type $HO(CH_2)_2O(CH_2)_wR^5$ can be introduced in the same way.

Scheme 3



In the case of phenyl derivatives it is better to start from a compound of type **S**, whereas PG' represents a suitable protecting group. Amide coupling with *N*-methylaniline leads to a derivative of type **T**, then deprotection to a derivative of type **U**. Ether bond formation, via a *Mitsunobu*-type reaction or from a correponding alkyl halide, leads to a compound of type **V**. Reduction leads to an aldehyde of type **W**, then reductive amination to an amine of type **X**. An alcohol of type $HO(CH_2)_2O(CH_2)_wR^5$ can be introduced in the same way.

Scheme 4

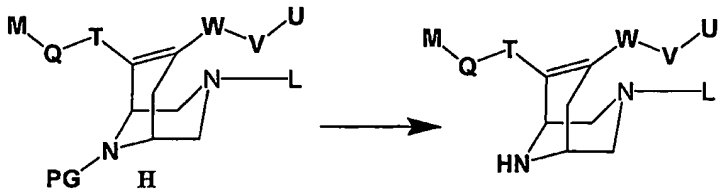


Preparation of final compounds

From precursors prepared as described above, the final compounds can be prepared using parallel chemistry techniques. For the specific examples, see the experimental part.

Diazabicyclononenes of type of **H** can be deprotected using standard procedures (Scheme 5). Purification by preparative HPLC gives the corresponding TFA salts or formate salts.

Scheme 5



The following examples serve to illustrate the present invention in more detail. They are, however, not intended to limit its scope in any manner.

Examples

Abbreviations

ACE	Angiotensin Converting Enzyme
Ang	Angiotensin
aq.	aqueous
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine serum albumine
Bu	Butyl
BuLi	*n*-Butyllithium
conc.	concentrated
DIBAL	Diisobutyl aluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC·HCl	Ethyl-*N,N*-dimethylaminopropylcarbodiimide hydrochloride
EIA	Enzyme immunoassay
Et	Ethyl
EtOAc	Ethyl acetate
FC	Flash Chromatography
HOBt	Hydroxybenzotriazol
MeOH	Methanol
org.	organic
PG	protecting group
RAS	Renin Angiotensin System
rt	room temperature
sat.	saturated
sol.	Solution
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl

TEMPO	2,2,6,6-Tetramethylpiridine-1-oxyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

Preparation of the precursors

(*rac.*)-(*1R, *5S**)-8-Methyl-3-trifluoromethanesulfonyloxy-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (B1)**

A sol. of compound 8-methyl-3-oxo-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester (Majewski, M., Lazny, R., *J. Org. Chem.*, **1995**, *60*, 5825, 1.81 g, 9.12 mmol) in THF (35 mL) was cooled to 0 °C and NaH (about 60% in mineral oil, 435 mg, about 10.0 mmol) was added. A gas evolution was observed. After 20 min, Tf_2NPh (3.86 g, 10.8 mmol) was added. 10 min later, the ice bath was removed. The sol. was stirred overnight, and diluted with EtOAc and washed with brine (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC yielded the title compound (2.37 g, 78%).

(*rac.*)-(*1R, *5S**)-9-Methyl-7-trifluoromethanesulfonyloxy-3-thia-9-aza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid methyl ester (B2)**

A sol. of LDA was prepared from diisopropylamine (5.8 mL, 41.2 mmol), BuLi (1.6 M in hexanes, 26.2 mL, 42.0 mmol) and THF (60 mL). This sol. was cooled to –78 °C and a sol. of 9-methyl-3-thia-9-azabicyclo[3.3.1]nonan-7-one (Jerchel, D; *et al.*; *Justus Liebigs Ann. Chem.*, **1957**, *607*, 126; Zirkle, C. L.; *et al.*; *J. Org. Chem.*, **1961**, *26*, 395, 6.42 g, 37.5 mmol) in THF (70 mL) was added dropwise over 3 min. The reaction mixture was stirred for 3 h at -78 °C, then methylcyanoformat (3.87 mL, 48.9 mmol) was added. The reaction mixture was stirred for 1 h at -78 °C and a sol. of $AgNO_3$ (9.12 g, 53.7 mmol) in H_2O/THF (1:1, 70 mL) was added. After 10 min, H_2O (35 mL) and AcOH (35 mL) were added and the reaction mixture was allowed to warm to rt. Ammoniac (25% in water, 120 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (2x). The combined org. extracts were dried over $MgSO_4$ and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the intermediate methyl ester (7.59 g, 88%).

A sol. of bicyclononanone former product (550 mg, 2.40 mmol) in THF (10 mL) was cooled to 0 °C and NaH (about 60% in mineral oil, 144 mg, about 3.60 mmol) was added.

A gas evolution was observed. After 20 min, Tf_2NPh (1.11 g, 3.12 mmol) was added. 10 min later, the ice bath was removed. The sol. was stirred overnight, and diluted with EtOAc and washed with brine (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC yielded the title compound as an oil (667, 77%).

(*rac.*)-(*1R, *5S**)-9-Methyl-7-trifluoromethanesulfonyloxy-3-oxa-9-aza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid methyl ester (B3)**

A mixture of NaH (0.91 g, 60% in oil, 21 mmol) and dimethylcarbonate (2.18 g, 24 mmol) in cyclohexane (16 mL) was heated to 60 °C under nitrogen. 9-Methyl-7-oxo-3-oxa-9-azabicyclo[3.3.1]nonane (Jerchel, D; *et al.*; *Justus Liebigs Ann. Chem.*, **1957**, *607*, 126; Zirkle, C. L.; *et al.*; *J. Org. Chem.*, **1961**, *26*, 395, 1.55 g, 10.0 mmol) was added, and the mixture was stirred at reflux for 2 h. The mixture was allowed to cool to rt, and ice and water were added. The phases were separated, and the org. phase was washed with water (1x). The combined aq. extracts were saturated with NH_4Cl, and extracted back with $CHCl_3$. The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the intermediate methylester (1.02 g, 48%).

A sol. of product obtained here above (4.67 g, 21.9 mmol) in THF (100 mL) was cooled to 0 °C and NaH (about 60% in mineral oil, 1.13 g, about 26 mmol) was added. A gas evolution was observed. After 20 min, Tf_2NPh (10.0 g, 28 mmol) was added. 10 min later, the ice bath was removed. The sol. was stirred overnight, and diluted with EtOAc and washed with brine (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC yielded the title compound as an oil (6.11 g, 81%).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-8-methyl-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (C1)**

A sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183, 16.47 g, 50.0 mmol) in THF (250 mL) was cooled to -78 °C. BuLi (1.6M in hexane, 31.0 mL, 50.0 mmol) was added. After 30 min, $ZnCl_2$ (1M in THF, 52 mL, 52 mmol, prepared from $ZnCl_2$ dried overnight at 150 °C and THF) was added. The mixture was allowed to warm up to rt. Vinyl triflate **B1** (7.90 g, 24.0

mmol) in THF (20 mL) and then $Pd(PPh_3)_4$ (500 mg, 0.43 mmol) were added. The mixture was heated tro reflux for 90 min and aq. 1M HCl (1 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title product (8.44 g, 82%).

(*rac.*)-(*1R, *5S**)-3-{4-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]phenyl}-8-methyl-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid methyl ester (C2)**

A sol. of [2-(4-bromophenoxy)ethoxy]-*tert*-butyldimethylsilane (patent application WO03/093267, 26.2 g, 79.0 mmol) in THF (450 mL) was cooled to -78 °C. BuLi (1.6M in hexane, 49.4 mL, 79.0 mmol) was added. After 30 min, $ZnCl_2$ (1M in THF, 85.3 mL, 85.3 mmol, prepared from $ZnCl_2$ dried overnight at 150 °C and THF) was added. The mixture was allowed to warm up to rt. Vinyl triflate **B1** (14.5 g, 44.0 mmol) in THF (50 mL) and then $Pd(PPh_3)_4$ (913 mg, 0.78 mmol) were added. The mixture was heated to 40 °C for 30 min, and aq. 1M HCl (1 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 2:98 → 4:96 → 10:90 → 15:85) yielded the title product (13.6 g, 71%).

(*rac.*)-(*1R, *5S**)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-9-methyl-3-thia-9-azabicyclo[3.3.1]non-6-ene-6-carboxylic acid methyl ester (C3)**

A sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183, 1.52 g, 4.61 mmol) in THF (20 mL) was cooled to -78 °C. BuLi (1.6M in hexane, 2.88 mL, 4.61 mmol) was added. After 30 min, $ZnCl_2$ (1M in THF, 5.00 mL, 5.00 mmol, prepared from $ZnCl_2$ dried overnight at 150 °C and THF) was added. The mixture was allowed to warm up to rt. Vinyl triflate **B2** (667 mg, 1.85 mmol) in THF (20 mL) and then $Pd(PPh_3)_4$ (107 mg, 0.093 mmol) were added. The mixture was heated to 50 °C for 30 min and aq. 1M HCl (1 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title product (818 mg, 96%).

(*rac.*)-(*1R, *5S**)-7-{4-[3-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-9-methyl-3-oxa-9-azabicyclo[3.3.1]non-6-ene-6-carboxylic acid methyl ester (C4)**

A sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, **1993**, *4*, 2183, 9.88 g, 30.0 mmol) in THF (200 mL) was cooled to -78 °C. BuLi (1.6M in hexane, 18.7 mL, 30.0 mmol) was added. After 30 min, $ZnCl_2$ (1M in THF, 30 mL, 30 mmol, prepared from $ZnCl_2$ dried overnight at 150 °C and THF) was added. The mixture was allowed to warm up to rt. Vinyl triflate **B3** (5.87 g, 17.0 mmol) in THF (30 mL) and then $Pd(PPh_3)_4$ (390 mg, 0.34 mmol) were added. The mixture was heated TO 40 °C for 30 min and aq. 1M HCl (1 mL) was added. The mixture was diluted with EtOAc and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title product (5.87 g, 77%).

(*rac.*)-(*1R, *5S**)-3-[4-(3-Hydroxypropyl)phenyl]-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester 2-methyl ester (D1)**

1–Chloroethyl chloroformate (7.98 g, 56.0 mmol) was added to a sol. of bicycloctene **C1** (8.07 g, 18.8 mmol) in 1,2-dichloroethane (120 mL). The sol. was heated to reflux. After 4 h, the reaction mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. MeOH (100 mL) was added. The mixture was stirred at 75 °C for 30 min, and the solvents were removed under reduced pressure. The residue was diluted with EtOAc and washed with aq. 1M NaOH (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was dissoled in CH_2Cl_2 (50 mL), DIPEA (4.70 g, 36.0 mmol) was added, and the mixture was cooled to 0 °C. Boc_2O (4.65 g, 21.0 mmol) was added and the mixture was stirred at 0 °C for 1 h, then at rt for 2 h. The mixture was washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (4.81 g, 64%).

(*rac.*)-(*1R, *5S**)-3-[4-(2-Hydroxyethoxy)phenyl]-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester 2-methyl ester (D2)**

1–Chloroethyl chloroformate (34.5 mL, 316 mmol) and $NaHCO_3$ (29.2 g, 348 mmol) were added to a sol. of bicycloctene **C2** (13.6 g, 31.6 mmol) in 1,2-dichloroethane (270 mL).

The sol. was heated to reflux. After 90 min, the reaction mixture was allowed to cool to rt, filtered, and the solvents were removed under reduced pressure. The residue was dried under high vacuum. MeOH (200 mL) was added. The mixture was stirred at 75 °C for 30 min, and the solvents were removed under reduced pressure. The residue was diluted with CH_2Cl_2, and washed with aq. 10% Na_2CO_3 (2x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was dried under high vacuum. The residue was dissolved in CH_2Cl_2 (270 mL), DIPEA (21.6 mL, 126 mmol) was added, and the mixture was cooled to 0 °C. Boc_2O (7.60 g, 34.8 mmol) was added and the mixture was stirred at 0 °C for 1 h, then at rt overnight. The mixture was washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:8 → 1:4 → 3:7 → 1:1 → 7:3 → EtOAc) yielded the title compound (5.66 g, 44%).

(*rac.*)-(*1R, *5S**)-7-[4-(3-Hydroxypropyl)phenyl]-3-thia-9-azabicyclo[3.3.1]-non-6-ene-6,9-dicarboxylic acid 9-*tert*-butyl ester 6-methyl ester (D3)**

1–Chloroethyl chloroformate (1.93 mL, 17.7 mmol) was added to a sol. of bicyclononene **C3** (818 mg, 1.77 mmol) and $NaHCO_3$ (1.49 g, 17.7 mmol) in 1,2-dichloroethane (20 mL). The sol. was heated to reflux. After 3 h, the reaction mixture was allowed to cool to rt, filtered, and the solvents were thoroughly removed under reduced pressure. MeOH (20 mL) was added and mixture was stirred at at 60 °C for 20 min. The mixture was allowed to cool to rt and the solvents were removed under reduced pressure. The residue was dissoled in CH_2Cl_2 (20 mL), DIPEA (1.82 mL, 10.6 mmol) was added, and the mixture was cooled to 0 °C. Boc_2O (1.16 g, 5.31 mmol) was added and the mixture was stirred at 0 °C for 30 min, then at rt for 30 min. The mixture was washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (586 mg, 76%).

(*rac.*)-(*1R, *5S**)-7-[4-(2-Hydroxypropyl)phenyl]-3,3-dioxo-3λ^6-thia-9-aza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-*tert*-butyl ester 6-methyl ester (D4)**

A sol. of compound **D3** (586 mg, 1.35 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C and 3-chloroperbenzoic acid (70%, 359 mg, 2.97 mmol) was added. The mixture was stirred at rt

for 2 h and 3-chloroperbenzoic acid (70%, 359 mg, 2.97 mmol) was added again. The mixture was stirred again for 2 h and was diluted with more CH_2Cl_2. The mixture was washed with aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (578 mg, 92%).

(*rac.*)-(*1R, *5S**)-7-[4-(3-Hydroxypropyl)phenyl]-3-oxa-9-azabicyclo[3.3.1]-non-6-ene-6,9-dicarboxylic acid 9-*tert*-butyl ester 6-methyl ester (D5)**

1–Chloroethyl chloroformate (5.90 g, 41 mmol) was added to a sol. of bicyclononene **C4** (5.72 g, 12.8 mmol) in 1,2-dichloroethane (75 mL). The sol. was heated to reflux. After 4 h, the reaction mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was diluted with MeOH (50 mL), and the mixture was stirred for 20 min at rt, then for 45 min at 80 °C. The solvents were removed under reduced pressure, and the residue was diluted with $CHCl_3$. This mixture was washed with aq. 1 M NaOH (1x), and brine (1x). The combined aq. extracts were extracted back with $CHCl_3$ (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was dissoled in CH_2Cl_2 (60 mL), DIPEA (3.18 g, 24.6 mmol) was added, and the mixture was cooled to 0 °C. Boc_2O (3.14 g, 14.4 mmol) was added and the mixture was stirred at 0 °C for 1 h, then at rt for 2 h. The mixture was washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (4.17 g, 78%).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester 2-methyl ester (E1)**

Tributylphosphine (1.61 mL, 7.2 mmol) was added to a sol. of bicycloctene **D1** (1.04 g, 2.59 mmol), 2-chloro-3,6-trifluorophenol (833 mg, 5.10 mmol) and azodicarboxylic dipiperidide (1.29 g, 5.10 mmol) in toluene (25 mL). The mixture was heated to reflux for 2 h and allowed to cool to rt. The solvents were removed under reduced pressure. Purification by FC yielded the title compound (1.11 g, 78%).

(*rac.*)-(*1R, *5S**)-3-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester 2-methyl ester (E2)**

PBu_3 (12.1 mL, 42 mmol) was added to a sol. of compound **D2** (5.56 g, 14.0 mmol), 2,6-dichloro-*p*-cresol (3.71 g, 21.0 mmol) and azodicarboxylic dipiperidide (5.30 g, 21.0 mmol) in toluene (120 mL). The mixture was heated to reflux for 1 h. The mixture was allowed to cool to rt, and the solvents were partially removed under reduced pressure. The residue was diluted with EtOAc. The mixture was washed with aq. 1M NaOH (2x), and the org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:9 → 2:8 → 3:7). yielded the title compound (5.95 g, 76%).

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3,3-dioxo-3λ^6-thia-9-azabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-*tert*-butyl ester 6-methyl ester (E3)**

Tributylphosphine (85%, 1.08 mL, 3.72 mmol) was added to a sol. of bicyclononene **D4** (578 mg, 1.24 mmol), 2-chloro-3,6-difluorophenol (407 mg, 2.48 mmol) and azodicarboxylic dipiperidide (626 mg, 2.48 mmol) in toluene (10 mL). The mixture was heated to reflux for 2 h and allowed to cool to rt. The solvents were removed under reduced pressure. Purification by FC yielded the title compound (668 mg, 88%).

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3-oxa-9-azabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-*tert*-butyl ester 6-methyl ester (E4)**

Tributylphosphine (7.05 g, 30.0 mmol) was added to a sol. of bicyclononene **D5** (4.04 g, 9.7 mmol), 2-chloro-3,6-difluorophenol (2.89 g, 17.5 mmol) and azodicarboxylic dipiperidide (7.05 g, 30.0 mmol) in toluene (80 mL). The mixture was heated to reflux for 2 h and allowed to cool to rt. The solvents were removed under reduced pressure. Purification by FC yielded the title compound (4.60 g, 84%).

(*rac.*)-(*1R, 5S*)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester (F1)**

Bicyclooctene **E1** (2.42 g, 4.40 mmol) was dissolved in EtOH (50 mL). Aq. 1M NaOH (40 mL) was added and the mixture was heated to 80 °C. The sol. was stirred for 5 h at 80 °C, then allowed to cool down to rt. After acidification to pH = 1-2 with aq. 1M HCl the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over

$MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (2.48 g, quantitative).

(*rac.*)-(*1R, 5S*)-3-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester (F2)**

A sol. of compound **E2** (5.95 g, 10.6 mmol) in EtOH (120 mL) was heated to 70 °C. Aq. 1M NaOH (95 mL) was added and the mixture was stirred at 70 °C. After 4 h the mixture was allowed to cool to rt. The solvents were partially removed under reduced pressure. The residue was diluted with EtOAc, and aq. 1M HCl was added to pH 1. The phases were shaken and separated. The aq. phase was extracted with EtOAc (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the title crude compound (5.88 g, quantitative yield).

(*rac.*)-(*1R, *5S**)-7-{4-[2-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3,3-dioxo-3λ^6-thia-9-azabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-*tert*-butyl ester (F3)**

Bicyclononene **E3** (668 mg, 1.09 mmol) was dissolved in EtOH (7 mL). Aq. 1M NaOH (3 mL) was added and the mixture was heated to 80 °C. The sol. was stirred for 5 h at 80 °C, then allowed to cool down to rt. After acidification to pH = 1-2 with aq. 1M HCl the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The residue was used further without purification (624 mg, 96%).

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3-oxa-9-azabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-*tert*-butyl ester (F4)**

Bicyclononene **E4** (4.60 g, 25 mmol) was dissolved in EtOH (200 mL). Aq. 1M NaOH (200 mL) was added and the mixture was heated to 80 °C. The sol. was stirred for 5 h at 80 °C, then allowed to cool down to rt. After acidification to pH = 1-2 with aq. 1M HCl the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (4.50 g, quantitative).

(*rac.*)-(*1R, *5S**)-2-({2-[3-(tert-Butyldimethylsilanyloxy)propoxy]-3-methyl-pyridin-4-ylmethyl}cyclopropylcarbamoyl)-3-{4-[3-(2-chloro-3,6-difluoro-phenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (G1)**

To a sol. of compound **F1** (3.45 g, 6.46 mmol) in CH_2Cl_2 (60 mL) were added the amine **R** (2.26 g, 6.46 mmol), DMAP (197 mg, 1.62 mmol), DIPEA (4.42 mL, 25.8 mmol), HOBt (1.30 g, 9.69 mmol), and EDC·HCl (3.09 g, 16.2 mmol). The mixture was stirred at rt overnight. EDC·HCl (2.00 g, 1.00 mmol) and DIPEA (3.50 mL, 20.4 mmol) were added. The mixture was stirred at rt for 3 days. Amine **R** (2.00 g, 5.71 mmol), EDC·HCl (2.00 g, 1.01 mmol), and HOBt (1.00 g, 7.40 mol) were added. After 2 days (total 6 days) the mixture was diluted with more CH_2Cl_2, washed with aq. 1M HCl (3x), and with aq. sat. $NaHCO_3$ (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7 → 2:4) yielded the title compound (3.43 g, 61%).

(*rac.*)-(*1R, *5S**)-2-({2-[3-(*tert*-Butyldimethylsilanyloxy)propoxy]-3-methyl-pyridin-4-ylmethyl}cyclopropylcarbamoyl)-3-{4-[2-(2,6-dichloro-4-methyl-phenoxy)ethoxy]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (G2)**

To a sol. of compound **F2** (3.50 g, 6.38 mmol) in CH_2Cl_2 (60 mL) were added the amine **R** (2.28 g, 6.38 mmol), DMAP (195 mg, 1.60 mmol), DIPEA (4.26 mL, 25.5 mmol), HOBt (1.29 g, 9.57 mmol), and EDC·HCl (3.06 g, 16.0 mmol). The mixture was stirred at rt overnight. EDC·HCl (2.00 g, 1.01 mmol), and DIPEA (3.50 mL, 21.0 mmol) were added. The mixture was stirred at rt for 3 days. Amine **R** (2.00 g, 5.60 mmol), EDC·HCl (2.00 g, 1.01 mmol), and HOBt (1.00 g, 7.40 mmol) were added. After 2 days (total 6 days) the mixture was diluted with more CH_2Cl_2, washed with aq. 1M HCl (3x), and with aq. sat. NaHCO3 (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure Purification of the residue by FC (EtOAc/heptane 1:4 → 3:7 → 2:4) yielded the title compound (2.95 g., 52%).

(*rac.*)-(*1R, *5S**)-6-({2-[3-(*tert*-Butyldimethylsilanyloxy)propoxy]-3-methyl-pyridin-4-ylmethyl}cyclopropylcarbamoyl)-7-{4-[3-(2-chloro-3,6-difluoro-**

phenoxy)propyl]phenyl}-3,3-dioxo-3λ6-thia-9-azabicyclo[3.3.1]non-6-ene-9-carboxylic acid *tert*-butyl ester (G3)

To a sol. of compound **F3** (2.23 g, 3.72 mmol) in CH_2Cl_2 (50 mL) were added the amine **R** (1.96 g, 5.59 mmol), DMAP (114 mg, 0.93 mmol), DIPEA (2.25 mL, 14.9 mmol), HOBt (757 mg, 5.59 mmol), and EDC·HCl (1.79 g, 9.32 mmol). The mixture was stirred at rt overnight. EDC·HCl (716 mg, 3.72 mmol) was added. After 2 days (total 3 days) the mixture was diluted with more CH_2Cl_2, washed with aq. 1M HCl (3x), and with aq. sat. NaHCO3 (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:99 → 2:98 → 3:97 → 4:96 →5:95 → 1:9) yielded the title compound (2.16 g., 62%).

(*rac.*)-(*1R, *5S**)-6-({2-[3-(*tert*-Butyldimethylsilanyloxy)propoxy]-3-methyl-pyridin-4-ylmethyl}cyclopropylcarbamoyl)-7-{4-[3-(2-chloro-3,6-difluoro-phenoxy)propyl]phenyl}-3-oxa-9-azabicyclo[3.3.1]non-6-ene-9-carboxylic acid *tert*-butyl ester (G4)**

To a sol. of compound **F4** (2.05 g, 3.72 mmol) in CH_2Cl_2 (50 mL) were added the amine **R** (1.96 g, 5.59 mmol), DMAP (114 mg, 0.93 mmol), DIPEA (2.25 mL, 14.9 mmol), HOBt (757 mg, 5.59 mmol), and EDC·HCl (1.79 g, 9.32 mmol). The mixture was stirred at rt overnight. EDC·HCl (716 mg, 3.72 mmol) was added. After 2 days (total 3 days) the mixture was diluted with more CH_2Cl_2, washed with aq. 1M HCl (3x), and with aq. sat. NaHCO3 (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:99 → 2:98 → 3:97 → 4:96 →5:95) yielded the title compound (3.00 g., 91%).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-2-{cyclopropyl-[2-(3-hydroxypropoxy)-3-methyl-pyridin-4-ylmethyl]-carbamoyl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (G5)**

To a sol. of **Example 1** (1.19 g, 1.82 mmol) in CH_2Cl_2 (5 mL) was added at 0°C DIPEA (0.80 mL, 4.56 mmol) and Boc_2O (0.61 g 2.74 mmol). The mixture was stirred at 0 °C for 30 min and was concentrated under reduced pressure . Aq. sat. NH_4Cl (5 mL) was added and the mixture was extracted with CH_2Cl_2 (3x),. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane = 1:1) yielded the title compound (1.09 g, 80%).

(*rac.*)-(*1R, *5S**)-2-{[2-(2-Carboxyethoxy)-3-methylpyridin-4-ylmethyl]cyclopropylcarbamoyl}-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (G6)**

To a sol. of compound **G5** (400 mg, 0.53 mmol) in CH_2Cl_2 (5 ml) containing TEMPO (0.4 mg) was added sat. aq. $NaHCO_3$ (0.22 mL) containing KBr (6.4 mg) and Bu_4NCl (7.8 mg). The mixture was cooled to 0°C and a sol. of NaOCl (2M, 1.2 ml), $NaHCO_3$ (0.56 mL) and brine (1.2 mL) were added dropwise over 45 min. The two layers were separated. The aq. extract was acidified with aq. conc. HCl, and extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 1:9) yielded the title compound (154 mg, 38%).

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-2-{cyclopropyl-[2-(2-methoxycarbonylethoxy)-3-methylpyridin-4-ylmethyl]-carbamoyl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (G7)**

A sol. of compound **G6** (110 mg 0.14 mmol) and Dowex $50H^+$ (0.13 g) in MeOH (5 mL) was stirred at rt for 24 h. After filtration the reaction mixture was concentrated under reduced pressure, and the crude title product was used in the next step without purification (70 mg, 64%).

(*rac.*)-(*1R, *5S**)-2-{[2-(2-Carbamoylethoxy)-3-methylpyridin-4-ylmethyl]-cyclopropylcarbamoyl}-3-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]-phenyl}-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (G8)**

A sol. of compound **G6** (70 mg; 0.09 mmol), EDC·HCl (44.6 mg, 0.228 mmol) and aq. NH_3 (25%, 0.10 ml) in CH_2Cl_2 (5 ml) was stirred at rt for 24h. The two layers were separated, and the aq. phase was extracted with CH_2Cl_2 (1x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 9:1) yielded the title compound (54 mg, 79%).

2-Chloro-N-phenylisonicotinamide (N)

To the sol. of 2-chloro-isonicotinoyl chloride (Anderson, W. K., Dean, D. C., Endo, T., *J. Med. Chem.*, **1990**, *33*, 1667, 10 g, 56.8 mmol) in 1,2-dichloroethane (100 mL) was added

at 0 °C a sol. of aniline (5.70 mL, 62.5 mmol) and DIPEA (10.2 ml, 59.6 mmol) in 1,2-dichloroethane (10 ml) during ca. 30 min. The reaction was stirred at 0 °C for ca. 30 min and subsequently for 1 h at 95 °C. Water (30 mL) was added at rt and the mixture was filtered-off. The filtrate was extracted with CH_2Cl_2 (200 mL). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was crystallized from MeOH/water 1:10 (110 mL), yielding the title compound (12.12 g, 92%). LC-MS: R_T = 0.87 min; ES^+ = 233.1.

2-Chloro-3-*N*-dimethyl-*N*-phenylisonicotinamide (O)

To a sol. of compound **N** (8.79g, 37.8 mmol) in THF (90 mL) was added BuLi (1.6M in hexane, 52 mL, 83.2 mmol) at –78°C. After 30 min MeI (7.70 mL, 124 mmol) was added dropwise at the same temperature. The mixture was stirred at –78 °C for 1 h, and was warmed up to 33 °C. The mixture was stirred at 33 °C for 30 min. Aq. 10% NH_4OH was added dropwise at rt, and the mixture was extracted with Et_2O. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. Purification by FC yielded the title compound (8.67 g, 88%). LC-MS:R_T = 0.85 min; ES^+ = 261.2.

2-Chloro-3-methylpyridine-4-carbaldehyde (P)

To the sol. of pyridine derivative **O** (9.58 g, 36.7 mmol) in CH_2Cl_2 (190 mL) was at –78 °C added DIBAL (1M in CH_2Cl_2, 55.1 mL, 55.1 mmol), and the mixture was stirred at –78 °C for 1.5 h. Aq. sat. tartaric acid monosodium monokalium salt in water (20 ml) was added and the mixture was allowed to warm up to rt. Water was added and the mixture was extracted with CH_2Cl_2. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC yielded the title compound (4.4 g, 77%). LC-MS:R_T = 0.76 min; ES^+ = 156.1.

(2-Chloro-3-methylpyridin-4-ylmethyl)-cyclopropylamine (Q)

A sol. of aldehyde **P** (4.70 g, 30.2 mmol) and cyclopropylamine (4.20 ml, 60.4 mmol) in MeOH (65 mL) was stirred at rt for 4 h. $NaBH_4$ (1.55 g, 39.2 mmol) was added and the mixture was stirred at rt for 12 h. Water and subsequently aq. 1M NaOH were added, and the solvents were partially removed under reduced pressure. The water phase was extracted with CH_2Cl_2 (2x). The combined org. extracts were dried over $MgSO_4$, filtered,

and the solvents were removed under reduced pressure. Purification of the crude by FC yielded the title compound (4.66 g, 79%). LC-MS:R_T = 0.43 min; ES^+ = 197.1.

{2-[3-(*tert*-Butyldimethylsilanyloxy)propoxy]-3-methylpyridin-4-ylmethyl}-cyclopropylamine (R)

A sol. of amine **Q** (1.24 g, 6.30 mmol) and 2-(*tert*-butyldimethylsilanyloxy)-propan-1-ol (403 mg, 10.1 mmol) in dioxan (5 ml) was heated at 115 °C for 12 h. The solvents were removed under reduced pressure, water was added, and the mixture was extracted with Et_2O (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC yielded the title compound (192 mg, 9%). LC-MS:R_T = 0.84 min; ES^+ = 351.4.

Preparation of the final compounds

Example 1

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide**

A sol. of compound **G1** (3.43 g, 3.95 mmol) in CH_2Cl_2 (35 mL) was cooled to 0 °C. HCl/dioxane (4M, 35 mL) was added. After 15 min the ice bath was removed nad the mixture was stirred for 1 h at rt. The solvents were rapidly removed under reduced pressure and the residue was dried under high vacuum for 15 min. The residue was then diluted with CH_2Cl_2 and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH_2Cl_2 5% → 10% → 15% → 20%) yielded the title compound (1.25 g, 48%).

Example 2

(*rac.*)-(*1R, *5S**)-3-{4-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-[2-(3-hydroxy-propoxy)-3-methylpyridin-4-ylmethyl]amide**

A sol. of compound **G2** (2.95 g, 3.34 mmol) in CH_2Cl_2 (30 mL) was cooled to 0 °C. HCl/dioxane (4M, 30 mL) was added. After 15 min the ice bath was removed and the mixture was stirred for 1 h at rt. The solvents were rapidly removed under reduced

pressure and the residue was dried under high vacuum for 15 min. The residue was then diluted with CH_2Cl_2 and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC ($MeOH/CH_2Cl_2$ 5% → 10% → 15% → 20%) yielded the title compound (1.32 g, 59%).

Example 3

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3,3-dioxo-3λ6-thia-9-azabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxypropoxy)-3-methylpyridin-4-ylmethyl]amide**

A sol. of compound **G3** (2.16 g, 2.32 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C. HCl/dioxane (4M, 25 mL) was added. After 15 min the ice bath was removed and the mixture was stirred for 1 h at rt. The solvents were rapidly removed under reduced pressure and the residue was dried under high vacuum for 15 min. The residue was then diluted with CH_2Cl_2 and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by by FC ($MeOH/CH_2Cl_2$ 6% → 8% → 10% → 15% → 20% → 30%) yielded the title compound (740 mg, 44%).

Example 4

(*rac.*)-(*1R, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3-oxa-9-azabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-[2-(3-hydroxypropoxy)-3-methylpyridin-4-ylmethyl]amide**

A sol. of compound **G4** (2.16 g, 2.32 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C. HCl/dioxane (4M, 25 mL) was added. After 15 min the ice bath was removed and the mixture was stirred for 1 h at rt. The solvents were rapidly removed under reduced pressure and the residue was dried under high vacuum for 15 min. The residue was then diluted with CH_2Cl_2 and washed with aq. 1M NaOH (1x). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by by FC ($MeOH/CH_2Cl_2$ 6% → 8% → 10% → 15% → 20% → 30%) yielded the title compound (1.06 g, 68%).

Example 5

(*rac.*)-(*1R, *5S**)-3-(4-{[(3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carbonyl)cyclopropylamino]methyl}-3-methyl-pyridin-2-yloxy)propionic acid**

A sol. of compound **G6** (70 mg) was stirred under N_2 in a HCl/Et_2O (2M, 2 mL) at rt overnight. The reaction mixture was concentrated and purified by HPLC (9.9 mg , 15 %).

Example 6

(*rac.*)-(*1R, *5S**)-3-(4-{[(3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carbonyl)cyclopropylamino]methyl}-3-methylpyridin-2-yloxy)propionic acid methyl ester**

A sol. of compound **G7** (70 mg) was stirred under N_2 in HCl/Et_2O (2M, 2 mL) at rt overnight. The reaction mixture was concentrated and purified by HPLC (13.3 mg, 20 %).

Example 7

(*rac.*)-(*1R, *5S**)-3-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid [2-(2-carbamoylethoxy)-3-methylpyridin-4-ylmethyl]cyclopropylamide**

A sol. of compound **G8** (50 mg) was stirred under N_2 in HCl/Et_2O (2M, 2 mL) at rt overnight. The reaction mixture was concentrated. Purification by HPLC yielded the title compound (35 mg, 76 %).

The following assay was carried out in order to determine the activity of the compounds of general formula **I** and their salts.

Inhibition of human recombinant renin by the compounds of the invention

The enzymatic in vitro assay was performed in 384-well polypropylene plates (Nunc). The assay buffer consisted of 10 mM PBS (Gibco BRL) including 1 mM EDTA and 0.1% BSA. The incubates were composed of 50 µL per well of an enzyme mix and 2.5 µL of renin inhibitors in DMSO. The enzyme mix was premixed at 4°C and consists of the following components:

- human recombinant renin (0.16 ng/mL)
- synthetic human angiotensin(1-14) (0.5 µM)
- hydroxyquinoline sulfate (1 mM)

The mixtures were then incubated at 37°C for 3 h.

To determine the enzymatic activity and its inhibition, the accumulated Ang I was detected by an enzyme immunoassay (EIA) in 384-well plates (Nunc). 5 µL of the incubates or standards were transferred to immuno plates which were previously coated with a covalent complex of Ang I and bovine serum albumin (Ang I – BSA). 75 µL of Ang I-antibodies in essaybuffer above including 0.01% Tween 20 were added and a primary incubation made at 4 °C overnight. The plates were washed 3 times with PBS including 0.01% Tween 20, and then incubated for 2 h at rt with an antirabbit-peroxidase coupled antibody (WA 934, Amersham). After washing the plates 3 times, the *peroxidase substrate* ABTS (2.2'-azino-di-(3-ethyl-benzthiazolinsulfonate), was added and the plates incubated for 60 min at room temperature. After stopping the reaction with 0.1 M citric acid pH 4.3 the plate was evaluated in a microplate reader at 405 nm. The percentage of inhibition was calculated of each concentration point and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC_{50}). The IC_{50}-values of all compounds tested are below 10 µM.

Examples of inhibition:

Example 1: 0.25 nM

Example 2: 0.18 nM

Example 3: 5.51 nM

Example 4: 0.55 nM

Example 5: 3.0 nM

Example 6: 6.7 nM

Example 7: 3.0 nM